Four and a half LIM protein 1: a novel chaperone for atrium-specific Kv1.5 channels with a potential role in atrial arrhythmogenesis

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Online publish-ahead-of-print 5 April 2008

This editorial is linked to the article 'Four and a half LIM protein 1: a partner of KCNA5 in human atrium' by Z. Yang et al., 2008, pp. 449–457, this issue.

Chronic atrial diseases are associated with electrical, mechanical, and structural changes (remodelling) that result from activation of diverse signal transduction pathways. In atrial fibrillation (AF), the high atrial rate abbreviates the atrial activation period, which is followed by reduced $I_{\text{Ca,L}}$ and increased inward-rectifier $K^+$ currents like the background current ($I_{K1}$) and a constitutively active form of the acetylcholine-dependent $K^+$ current ($I_{K,\text{ACH}}$). There is also evidence for AF-associated reduction in the ultra-rapid delayed-rectifier $I_{Kur}$, although the reported findings have been inconsistent and the underlying molecular mechanisms are less clear. Response rate to antiarrhythmic drugs is low with respect to termination of AF or maintenance of sinus rhythm, and many of the drugs lead to adverse effects including ventricular arrhythmias. Given these limitations, an alternative approach is to design drugs that target atrium-selective ion channels like $I_{Kur}$, which plays a role in AF pathophysiology but not in ventricular function. However, our knowledge of the cellular processes underlying normal regulation of $I_{Kur}$ are still incomplete.

In order to contribute to atrial function in a specific way, the different ion channels have to be in the right place at the right time. This is regulated by multiple cellular processes, such as gene transcription, protein translation, trafficking, and membrane localization. Further fine-tuning is achieved by accessory channel subunits and by post-translational protein modifications. Several findings have implicated accessory KChIP2$^+$ and Kvβ1$^+$ subunits, and scaffold proteins like PDS97$^+$ and cytoskeletal α-actinin$^+$, in regulation of $I_{Kur}$ or heterologously expressed $K^+$ currents derived from the principal $I_{Kur}$ channel α-subunit Kv1.5 (KCNA5). However, Kv1.5-based $K^+$ currents only partially reproduce the phenotype of native $I_{Kur}$, suggesting involvement of additional regulatory mechanisms.

Yang et al., 2008, provide strong evidence that four and a half LIM protein 1 (FHL1) may represent a novel regulator of human atrial Kv1.5 channels. Specifically, using glutathione-S-transferase (GST) fusion protein and mass spectrometry-based techniques, the authors identified FHL1 as a potential protein partner of human Kv1.5 channels. LIM domain proteins like FHL1 recruit specific proteins, segregate these partners to discrete subcellular locations, and modulate their activities or assemble them into multi-protein complexes.

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Ca$^{2+}$ channel complex in neurons.$^{10}$ Thus, it is possible that targeting protein kinases to Kv1.5 participates in the effects of FHL1. It is furthermore unclear whether FHL1-related alterations in current characteristics involve changes in expression and/or membrane trafficking of Kv1.5. Also, FHL1 is known to serve not only as an adaptor and localizer protein, but also to compete with and change the conformation of targeted proteins. Thus, it is likely that the influence of $I_{Kur}$ by FHL1 involves multiple contributing mechanisms. Further work is needed to identify the specific mechanism(s) by which FHL1 modulates $I_{Kur}$ function.

$I_{Kur}$ is an atrium-selective ion current with the potential of being a promising drug target for therapy of atrial arrhythmias without concomitant adverse effects in the ventricles.$^{11}$ However, experimental data on $I_{Kur}$ remodelling in AF patients are unequivocal, showing either unchanged or reduced $I_{Kur}$ amplitude.$^{1}$ These inconsistent findings are assumed to result from variations in expression and post-translational modifications (S-nitrosylation, degradation)$^{12,13}$ of Kv1.5 and from differences in underlying cardiac diseases and/or concomitant medication.$^{14}$ The results of Yang et al.$^{7}$ raise the intriguing possibility that differences in FHL1 expression or function may contribute to the inconsistent findings with $I_{Kur}$. Although the protein levels of FHL1 in patients with AF are currently unknown, a recent study performed in a porcine model of pacing-induced AF suggests that sustained AF is associated with an approximately five-fold and approximately three-fold increase in mRNA and protein levels of FHL1, respectively.$^{15}$ Although caution is needed when extrapolating these results to the clinical situation, this study suggests that at least in some AF patients increased FHL1 expression may counteract the down-regulation of Kv1.5, providing a plausible explanation for the inconsistent $I_{Kur}$ results in AF patients. This hypothesis warrants direct experimental verification in subsequent work.

**Funding**

Supported by the German Federal Ministry of Education and Research (BMBF) through the Atrial Fibrillation Competence NETwork (AFNET, grant 01Gi0204), by a grant from the Foundation Leducq and by an European Union grant (NORMACOR, LSHM-CT-2006-018676).

**Conflict of interest:** none declared.

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